

Case Reports

Cough Due to Captopril

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CAPTOPRIL is useful in treating hypertension and as an "unloading" agent in managing congestive heart failure. It acts by lowering peripheral resistance and may do this in three ways: by inhibiting the "converting enzyme" that governs the conversion of angiotensin I to angiotensin II, by enhancing kinin levels (by inhibiting kininase II) and by influencing prostaglandin metabolism. The relative importance of these three mechanisms is not known but seems to vary with volume-renin state, the concomitant use of other drugs and undefined factors.¹

Captopril therapy is useful because it is effective in most patients, is relatively well tolerated and lacks the side effects of many other antihypertensive drugs now available. The drug is, however, not without its problems.²⁻⁸ Rash (5% to 10%), dysgeusia (4% to 7%) and gastrointestinal symptoms are its most common side effects, and neutropenia (0.2%) and proteinuria (1.2%) are rare complications. Renal failure is a hazard in patients with preexisting renal disease, especially renovascular disease. Side effects generally disappear when captopril use is discontinued and most seem dose-related, being less frequent at lower doses and often subsiding, despite continuation of therapy, when the dosage is reduced.³ Recent work suggests that doses used in earlier studies may have been unnecessarily high.³

Cough due to captopril use has been reported in only a few series,^{2,4-8} and the US manufacturer, Squibb, has had only desultory reports of this side effect (W. G. Jump, PharmD, E. R. Squibb, written communication, July 1985). Review of the published reports, however, suggests it is not uncommon, and my own experience is consistent with this impression. Cough has recently been described also with the use of enalapril maleate, a recently released, long-acting, angiotensin-converting enzyme inhibitor.⁹

I report four cases of cough almost certainly due to the use of captopril.

Reports of Cases

Case 1

The patient, a 59-year-old businessman, was seen in January 1985 because of cough. He had had hypertension for 25 years, but renal function was normal and he had no heart disease.

In March 1984, in the course of a routine medical evaluation, results of a pulmonary examination were normal and a chest film was negative. A spirogram was normal, with a forced vital capacity (FVC) of 3.85 liters (98% predicted), forced expiratory volume in one second (FEV₁) of 3.23 liters

(84% of FVC) and a normal flow-volume loop. The pulmonary history was negative for smoking, asthma, frequent pulmonary infections and for chronic or recurrent cough until January 1984, when he had a respiratory tract infection complicated by severe sinusitis and otitis requiring myringotomies and, in August of the same year, antrastomies. A purulent postnasal drip, which had caused a nocturnal cough, cleared a few weeks after antrastomy.

In August 1984 his blood pressure was poorly controlled by a regimen of propranolol hydrochloride and hydralazine hydrochloride in daily doses of, respectively, 320 mg and 200 mg. On this regimen, he did not cough. Hydralazine therapy was then stopped and captopril, 75 mg a day, substituted for it; propranolol therapy was continued.

In October 1984 he consulted a chest physician because of a dry, almost incessant cough beginning several weeks earlier that interfered with sleep and with telephoning (an occupational necessity). Findings on pulmonary examination were normal. Methacholine challenge spirometry showed FVC and FEV₁ values of, respectively, 3.66 and 3.07 liters (control), 3.43 and 2.89 liters after inhaled saline and 2.89 and 2.64 liters after 50 mg per ml of methacholine was inhaled, the drop in FEV₁ (3.07 to 2.64 liters) being 14% (a 20% drop is considered normal clinically). His cough exacerbated during the test but was immediately relieved by inhaling tebutaline sulfate. On the presumption that bronchospasm was causing the cough, a trial of prednisone, 30 mg a day, was given and his other medication regimen continued. The cough promptly disappeared but recurred when the prednisone dose was tapered after ten days. The propranolol regimen was then stopped and verapamil, 360 mg daily, substituted for it. The captopril use was continued, and his cough persisted unchanged.

From November 1984 to June 1985, the use of captopril (75 to 300 mg daily) was continued, and clonidine, spirone-lactone and metoprolol tartrate in various doses were combined with it. Cough continued unchanged except when captopril therapy was discontinued for two days, whereupon it disappeared within 24 hours and then reappeared two days after the drug therapy was restarted.

On June 4, 1985, his hypertensive daughter (case 2 below) told him that a hacking cough had developed shortly after she started taking captopril and that this cough had disappeared a few days after stopping it. When he reported this anecdote to me, he was advised to stop the captopril therapy immediately. Within a few days his cough had almost disappeared and, within three weeks, it had subsided completely.

On June 17, 1985, a regimen of labetalol hydrochloride was begun as his sole antihypertensive agent. A few weeks later, with a dose of 500 mg daily, a very slight cough appeared. This cough subsided in a few weeks without a change in medication and, as of October 2, 1985, it had not recurred.

At no point in his course had he been short of breath.

Case 2

This 25-year-old woman was the daughter of the patient in case 1. I did not examine or treat her but only interviewed her by telephone. She had had mild hypertension for several years. There was no history of heart or kidney disease, and

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ABBREVIATIONS USED IN TEXT

FEV₁ = forced expiratory volume in one second
FVC = forced vital capacity

she said she did not have chronic cough, asthma or significant lung disease and had never smoked. Initially she was treated with a regimen of propranolol (dose unknown) and thiazide. On this regimen she had no cough. Because it was ineffectual, propranolol therapy was stopped and captopril, 75 mg per day, substituted. A few days after she started taking captopril a cough developed that was dry, incessant and intolerable. She was not short of breath. After a month, she stopped taking the drug; a few days later, her cough disappeared. Treatment with atenolol, 50 mg per day, was then begun. Her blood pressure control has been excellent since and her cough has not recurred.

Case 3

This patient, a 63-year-old businessman, was seen January 1984 with thalamic stroke and untreated hypertension. Renal function was normal and there were no findings of heart disease other than minimal, nonspecific electrocardiographic repolarization abnormalities. He said he did not have cough or dyspnea and his chest film in October 1984 had been normal; he had smoked cigars and pipe only until eight years before, and a mild cough disappeared then and did not recur.

He was initially treated with β -blockers (propranolol, 80 mg a day, then nadolol, 40 mg a day), but this therapy was stopped because of depression; he did not cough while receiving these drugs. In April 1985, therapy with captopril, 75 mg a day, was begun and a week later the dose was increased to 100 mg a day. Blood pressure control was excellent. On July 8, 1985, he reported a dry, incessant cough that kept him awake; it had begun about a month earlier. He was not short of breath. Cardiopulmonary examination showed no abnormalities. Methacholine challenge spirometry showed FVC and FEV₁ values of, respectively, 2.49 liters (80% of predicted) and 2.36 liters (95% of FVC), controls; 2.40 and 2.11 liters after inhaling saline, and 2.53 and 2.09 liters after inhaling 50 mg of methacholine, the decrease in the FEV₁ (2.36 to 2.09 liters) being 10% (a 20% drop considered normal clinically); neither dyspnea nor cough occurred with the test.

The use of captopril was then discontinued, and the cough subsided in 72 hours. On July 20, 1985, at his own insistence, the captopril therapy was resumed. Within three days his cough had recurred. A few days later he stopped taking the drug, and again within three days the cough subsided.

Nifedipine was then given with good blood pressure control and no significant side effects. His cough did not recur.

Case 4

This 56-year-old woman presented in mid-January 1985 with dilated cardiomyopathy. She complained of dyspnea, angular chest pain and fatigue with effort. She had for some time been taking digoxin and a diuretic. In February 1985 a regimen of captopril, 37.5 mg a day, was begun and a month later the dose was increased to 75 mg a day. Her dyspnea was much relieved. On May 23, 1985, she mentioned a slight dry cough that had begun about two weeks earlier. This was attributed to left ventricular failure and the dosage of captopril was increased again, to 100 mg a day. On August 21, 1985, her condition was stable in every way but she again

noted dry cough that had worsened and had now become very annoying. Aware now that the use of captopril can cause cough, I stopped the drug therapy abruptly. Within three days the cough was "much better" and on September 10 it was gone. After discontinuing the captopril regimen, her effort dyspnea gradually worsened but she felt otherwise about the same.

Discussion

In these four patients, cough began a few days to weeks after captopril therapy was started (see Table 1), persisted until the drug regimen was stopped and then subsided quickly, with remarkable improvement in two or three days and complete disappearance in no more than a few weeks. Doses were average. The cough was dry, mild to moderate in severity, but intolerable in three patients because it kept them awake and, in one of these three, also precluded phone conversations necessary in his work. No patient was short of breath.

There is little doubt that cough in these four patients was indeed due to the use of captopril. Especially convincing was case 3, in which the patient's cough recurred when he resumed taking captopril and disappeared when the therapy was stopped the second time. This response occurred also in the case reported by Sesoko and Kaneko, in which the drug therapy was resumed and discontinued twice. None of the four patients in the cases reported here had cough before or after the captopril experience except in case 1 in which the patient had a transient, slight cough with a regimen of labetalol (though he had had none with a large dose of propranolol).

The frequency of cough due to captopril therapy is not established, but the scant published data suggest it occurs in about 5% to 15% of patients treated for a long time with the drug, an estimate consistent with my experience. If this estimate is correct, cough may well be the most common side effect of this drug. Havelka and co-workers cite 4 cases of 67 patients treated over a long term with a regimen of captopril, with disappearance of cough within three weeks of stopping the drug therapy in the one patient who did so.⁴ Forslund and associates mention cough in one of ten patients but give no details.⁵ Knoben reports 45 cases in which 7 patients had cough that, in all 7, subsided within a few days of stopping the captopril therapy and recurred within a few days of resuming it.⁷ In three cases, cough was so severe that the drug therapy had to be stopped. My own experience of finding two new cases within three months of being alerted to the problem (by the first two patients) suggests that cough is rather a common side effect of administration of the drug. Yet Frohlich and colleagues, in their extensive review of the captopril experience, do not mention cough as a side effect.³

The cause of cough in these patients is not clear. Congestive heart failure is unlikely: three had no heart disease, no dyspnea and no signs of congestive heart failure at the height of their cough; and case 4 (with cardiomyopathy) was, in fact, *less* breathless while on a regimen of captopril than after stopping it. Pulmonary infiltrates were unlikely, in view of the lack of physical signs and the rapid disappearance of symptoms on discontinuing taking the drug, but chest films were not done and this source cannot be ruled out.

Bronchial irritability is theoretically an attractive explanation of captopril-induced cough. This drug inhibits the angiotensin-converting enzyme, which is identical to (pulmonary) kininase II. Kininase II governs the catabolism of bradykinin,

TABLE 1.—Clinical Characteristics of Patients on Captopril Therapy

Case	Age, Years	Sex	Diagnosis	Heart Disease	Lung Disease	Captopril Dose, mg/d	Remarks
1 . . .	59	♂	Hypertension	No	No	75	No cough with β -blocker
2 . . .	25	♀	Hypertension	No	No	75	No cough with β -blocker
3 . . .	63	♂	Hypertension	No	No	100	No cough with β -blocker
4 . . .	56	♀	Cardiomyopathy	Yes	No	75	Dyspnea less with captopril

and inhibition of this enzyme would be expected to increase bradykinin levels in the lung.^{1,10} This increase might affect the lung by directly inducing smooth muscle contraction, by promoting local edema or by irritating nerve endings. By stimulating phospholipase, bradykinin could augment formation of the arachidonic acid derivatives, prostaglandins and leukotrienes, which may be etiologically important in asthma,^{1,11} and it may also directly affect release of histamine from mast cells, an action thus far shown, however, only in murine mast cells in vitro. Inhaling bradykinin can provoke bronchospasm, but only in patients with asthma¹²; none of the patients in the cases reported here had asthma.

In case 1, bronchial irritability is suggested by the exacerbation of cough by methacholine and its termination with the use of the β_2 agonist, terbutaline, during the methacholine challenge; by the unequivocal relief of cough with the administration of prednisone, and, perhaps, by his slight cough on labetalol therapy alone. At the height of his captopril cough, however, he was not short of breath with effort, had no physical signs of bronchospasm and spirometry results were only slightly, if at all, positive for bronchospasm before or after methacholine challenge. Moreover, his cough while receiving a substantial dose of labetalol was mild and transient, whereas the captopril-associated cough had been insufferable; indeed, he had had no cough at all while taking propranolol, 320 mg daily. The patient in case 3 had no cough with substantial doses of both propranolol and nadolol, but a severe cough developed on two occasions with the use of captopril; his spirogram findings were also unimpressive. The patient in case 2 had no cough on an atenolol regimen of 50 mg a day.

A practical implication of this experience is that, in patients in whom cough develops while on captopril therapy, β -blockers need not be withheld on the presumption of provokable bronchospasm.

Cough due to captopril therapy is not common and is probably idiosyncratic. Its concurrence in father and daughter (cases 1 and 2), therefore, suggests a genetic determination.

Captopril may be easily overlooked as the cause of cough. In a patient with heart failure "unloaded" with captopril therapy, cough is likely to be ascribed to the failure itself and the drug therapy continued or even increased, as initially in the patient in case 4. In a hypertensive patient taking a β -blocker and captopril, cough is likely to be attributed to the β -blocker, as in case 1, or to occult heart failure, whereupon the captopril dose might be increased.

Prospective studies can establish how often captopril causes cough, which patients are likely to get it, the role of dose and possibly even the cause. Such studies are feasible because this excellent drug is often used and cough, when it

occurs, does so soon after starting captopril therapy and subsides promptly on stopping it.

Addendum

Since this report was submitted, three other cases of captopril-induced cough have come to my attention. The first was of a 70-year-old woman with hypertension in whom a severe cough without dyspnea or wheezing promptly developed with the use of captopril, 50 mg per day, and whose cough completely disappeared two days after stopping the therapy several weeks after beginning it. The second case was of a 72-year-old woman with hypertension and ischemic heart disease complicated by mild congestive heart failure and mild mitral regurgitation who, in 1982, while receiving an unknown dose of captopril, had a cough develop that cleared completely five days after the drug therapy was stopped. In November 1984, after captopril therapy was resumed at 75 mg daily, a cough developed that disappeared a few days after she stopped taking the drug. The third patient, a 63-year-old woman with hypertension and a questionable history of asthma, had the development of an annoying cough without dyspnea on a regimen of captopril, 75 mg daily. The cough cleared over a two-week period after stopping the regimen; she is currently under investigation for airways disease.

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Stress-Induced Cessation of Lactation

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ANECDOTAL REPORTS of abrupt cessation of lactation due to psychological stress are well known in folk experience. In this paper I describe the cases of two women who had abrupt cessation of lactation and of colostrum excretion, respec-

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